Institution: Queen Mary University of London		
Unit of Assessment: 1		
Title of case study: Cladribine as a Novel Treatment for Multiple Sclerosis		
Period when the underpinning research was undertaken: 2006-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
1) Gavin Giovannoni	1) Professor of Neurology	1) 11/2006 - present
2) Klaus Schmierer	2) Professor of Neurology	2) 09/2009 - present
3) David Baker	3) Professor of Neuroimmunology	3) 11/2006 - present
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum of 100 words)

Queen Mary's neuroscience research team have developed, de-risked and discovered the mode of action of cladribine, a new highly-effective oral disease-modifying therapy to treat relapsing multiple sclerosis (MS). MS is the commonest non-traumatic disabling disease of the nervous system to affect young adults, with socio-economic impacts such as unemployment and reduced quality of life. Cladribine tablets (Mavenclad®) were approved as a New Drug Agent by the European Medicines Agency (EMA) in August 2017, by NICE for use in the UK in November 2017 and by the FDA in 2019. Cladribine tablets have now been licenced in over 80 countries. Since the drug is given orally, in short courses, and has a very low monitoring and adverse event profile, it was one of only two therapeutic innovations to be selected by the NHS accelerated access collaborative in 2018.

2. Underpinning research (indicative maximum of 500 words)

Multiple sclerosis (MS) affects about 3,000,000 people worldwide, including 1 in 300-800 people in the United Kingdom. The immune system drives the production of damaging neurological attacks that lead to permanent disability. This leads to socioeconomic issues relating to unemployment and reduced quality of life. Relapsing MS (RMS) is the commonest type, with 85% of individuals with MS diagnosed with RMS. RMS is two to three times more common in women than men. Research in Queen Mary's Centre for Neuroscience has focused on developing a protocol for the off-label preparation of cladribine for use in patients with RMS who do not fulfil NHS England criteria for treatment with licensed disease modifying drugs [3.1]. Cladribine is a small molecule purine analogue that was originally licensed to treat hairy cell leukaemia. The research has addressed the following questions:

Efficacy: (1) Prof. Giovannoni is the international principal investigator (PI) of the oral cladribine phase 3 development programme. Giovannoni helped Serono, a pharmaceutical company, acquired by Merck in 2006, do due diligence on the in-licensing of a patented oral formulation of cladribine for clinical development. As PI and member of the trial steering committee, Giovannoni first helped model pharmaco-kinetic and pharmaco-dynamic data from the intravenous formulation of cladribine to select an oral dose range for clinical development (data on file at Merck). Giovannoni then helped design and write the trial protocol for a large phase 3 trial of cladribine tablets in RMS. The trial showed that cladribine is a highly effective disease-modifying therapy (DMT) to treat RMS, with relative risk reductions in the annualised relapse rates of 57.6% and 54.5% for the two doses of cladribine studied compared to placebo [3.2].

(2) A post-hoc analysis of the phase 3 trial was done that showed that a subgroup of patients with highly-active relapsing-remitting MS had a greater response to cladribine tablets [3.3]. In addition, the 3- and 4-year results of the blinded extension study showed that just 2 short courses of treatment over 2 years resulted in the majority of patients staying in remission in years 3 and 4, ie without the need for additional treatment [3.4].

Safety: Prof. Schmierer performed a meta-analysis of malignancies in all phase 3 trials of DMTs in RMS and showed that cladribine was not associated with an increased risk of malignancies [3.5]. The meta-analysis showed that due to zero cases in the placebo arm of the phase 3 trial of cladribine tablets, the perceived malignancy risk represented a false positive signal [3.5]. This

study was instrumental in convincing Merck-Serono to reconsider oral cladribine as a licensed treatment for RMS.

Mode of action: Prof. Baker led on detailed immunological studies performed at Queen Mary that have delineated that the mode of action of cladribine in people with RMS is via the prolonged suppression of peripheral memory B cells [3.6]. This has led the team to define a new class of MS DMTs called immune reconstitution therapies, and facilitated the adoption of cladribine tablets as a highly effective, safe and easy to use and monitor DMT for highly active RMS.

Thus, Queen Mary's research has led to the use of cladribine tablets to treat attacks ("relapses") and prevent disability in people with RMS, some of whom may even be considered cured given their long-term freedom of disease-activity without further treatment intervention. This has allowed wider international access to an affordable generic formulation of cladribine, enabling people with MS in lower and middle-income countries access to effective disease modifying treatment.

3. References to the research (indicative maximum of six references)

[3.1] Mao, Z., Álvarez-Gonzalez, C., De Trane, S., Yildiz, O., Albor, C., Doctor, G., Soon, D., Pepper, G., Turner, B. P., Marta, M., Mathews, J., Giovannoni, G., Baker, D. & Schmierer, K. (2018). Cladribine: Off-label disease modification for people with multiple sclerosis in resource-poor settings? *Multiple Sclerosis Journal – Experimental, Translational and Clinical, 4* (2). https://doi.org/10.1177/2055217318783767

[3.2] Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Sørensen, P. S., Vermersch, P., Chang, P., Hamlett, A., Musch, B., Greenberg, S. J. & The CLARITY Study Group. (2010). A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *The New England Journal of Medicine, 362* (5), 416-426. https://doi.org/10.1056/NEJMoa0902533

[3.3] Giovannoni, G., Sorensen, P. S., Cook, S., Rammohan, K. W., Rieckmann, P., Comi, G., Dangond, F., Hicking, C. & Vermersch, P. (2019). Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. *Multiple Sclerosis Journal, 25* (6), 819-827. https://doi.org/10.1177/1352458518771875

[3.4] Giovannoni, G., Sorensen, P. S., Cook, S., Rammohan, K., Rieckmann, P., Comi, G., Dangond, F., Adeniji, A. K. & Vermersch, P. (2017). Safety and Efficacy of Oral Cladribine in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the randomised Extension Trial of the CLARITY Study. *Neurology, 24* (12), 1594-1604. https://doi.org/10.1177/1352458517727603

[3.5] Pakpoor, J., Disanto, G., Altmann, D. R., Pavitt, S., Turner, B. P., Marta, M., Juliusson, G., Baker, D., Chataway, J., Schmierer, K. (2015). No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. *Neurology: Neuroimmunology & Neuroinflammation*, *2* (6), e158. https://doi.org/10.1212/NXI.0000000000000158

[3.6] Ceronie, B., Jacobs, B. M., Baker, D., Dubuisson, N., Mao, Z., Ammoscato, F., Lock, H., Longhurst, H. J., Giovannoni, G. & Schmierer, K. (2018). Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells. *Journal of Neurology, 265* (5), 1199-1209. https://doi.org/10.1007/s00415-018-8830-y

4. Details of the impact (indicative maximum of 750 words)

Queen Mary's neuroscience research has resulted in the successful repurposing of cladribine, a small molecule purine analogue originally licensed to treat hairy cell leukaemia, into an oral formulation to treat patients with highly active relapsing MS (RMS).

Access to effective, affordable treatment for patients with active RMS

In the NHS

Following Merck's withdrawal of cladribine from the market in 2011 due to concerns about cancer as a side effect, Queen Mary's neuroscience team has focused on generating an evidence base to alleviate these concerns. They presented the licencing package to the European Medicines Agency (EMA) and the oral variant was approved as a New Drug Agent in August 2017 [5.1, 5.2]. This was approved for use in the UK and US following a NICE appraisal in November 2017 [5.3] and by the FDA in 2019 [5.4] respectively, based on the team's evidence [3.1]. This is a novel global medicine sold under the trade name Mavenclad® by Merck [5.5].

Cladribine tablets are given as short courses (up to 20 days of treatment over 4 years), are well tolerated, have very few adverse effects, and therefore have a low monitoring burden. Both the brevity of the active intervention and the fact the medicine can be taken at home aid treatment adherence. Thus, there is potential to significantly increase access to treatment for patients with RMS and at the same time reduce healthcare utilisation. Cladribine tablets are also the only capsule in the range of disease modifying drugs that does not contain beef gel, making it suitable for vegetarians and Hindus, thereby providing greater scope for personalisation of treatments [5.6]. As a result of these favourable attributes, in October 2018, the NHS named cladribine tablets a 'rapid uptake' product to be made accessible to more patients through the Accelerated Access Collaborative (AAC) [5.7]. The AAC identifies, and then actively supports the adoption of innovations that have the potential to transform the care of NHS patients. This adoption made the drug available to over 50,000 patients and provided cost savings to the NHS of GBP30,000,000 [5.8]. It is one of only two therapeutic innovations to be prioritised as part of the AAC in 2018. Queen Mary, in partnership with the UCL Partners Academic Health Science Network, has designed a national programme to promote the rapid adoption of cladribine tablets. So far, over 24,000 patients globally have been treated with cladribine tablets [5.5].

In resource-poor settings
The Queen Mary developed off-label protocol [5.9] for using generic subcutaneous cladribine for patients with active RMS who do not fulfil NHS England criteria for treatment with licensed treatments. This protocol has been published, widely disseminated, and is now being used by clinicians in resource-poor countries to treat people with RMS. This has enabled affordable access to cladribine as a treatment for RMS in low- and middle-income countries. In total, cladribine tablets have now been licenced in over 80 countries worldwide [5.5].

Cost savings for the NHS
The use of generic cladribine for treating RMS has led to substantial savings for the NHS. The cost of treatment is GBP1,300 (20 x GBP65/10mg cladribine maximum dose) compared to GBP56,360 for alemtuzumab (8 x GBP7,045), excluding the costs of monthly monitoring for 4 years after the last dose, and management of the secondary autoimmunities which occur in 30-50% of people treated, as a side-effect of this treatment.

Commercial success of cladribine tablets (Mavenclad®)
In 2018, Merck reported a 42% decline in net income to EUR247,000,000 for Q2, but the new drug Mavenclad helped the company maintain organic sales growth, bringing in a revenue of USD23,000,000 [5.10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] electronic medicines compendium. (2017). *Summary of Product Characteristics, Mavenclad 10mg tablets*. https://www.medicines.org.uk/emc/product/8435/smpc#gref

[5.2] European Medicines Agency: Science, medicines, health. (2017). *Mavenclad, cladribine*. https://www.ema.europa.eu/en/medicines/human/EPAR/mavenclad

[5.3] NICE. (2017). *Cladribine tablets for treating relapsing–remitting multiple sclerosis*. https://web.archive.org/web/20190803170131/https://www.nice.org.uk/guidance/ta493

[5.4] US Food and Drug Administration. (2019). *Mavenclad (cladribine), full prescribing information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022561s000lbl.pdf

[5.5] A. N. Paterson. Senior Vice President, Head of US and Global MS Franchise. *EMD Serono Inc* (testimonial letter, 23 October 2020). [Corroborator 1]

[5.6] M. Roberts. Head of Health Professionals Programmes. *MS Trust* (testimonial letter, 1 June 2020). [Corroborator 2]

[5.7] NHS. (2018). *NHS Accelerated Access Collaborative: Rapid uptake products. Cladribine (Mavenclad)*.

[5.8] Morelli-Green, J. (2018, 29 October). *More patients to access MS treatment through Government scheme*. Enviva Complex Care.

[5.9] Barts Health NHS Trust. (2015). *BartsMS Patient Information Sheet, Cladribine for treatment of people with multiple sclerosis*. https://multiple-sclerosis-research.org/2016/01/bartsms-off-label-cladribine-use-information-sheet/

[5.10] Underwood, G. (2018, 10 August). *Merck profits decline but new drugs maintain sales growth*. PharmaTimes online. http://www.pharmatimes.com/news/merck_profits_decline_but_new_drugs_maintain_sales_growth_1248405. Accessed 30 March 2020.